THE ENDOCRINOLOGY AND PATHOPHYSIOLOGY OF ALCOHOLIC CIRRHOSIS AND FUNCTIONAL RENAL FAILURE—A REVIEW

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The pathophysiology and characteristics of decompensated alcoholic cirrhosis and functional renal failure are reviewed. The review will be restricted to *alcoholic* cirrhosis, because most cases of functional renal failure in the United States occur in the setting of alcoholic cirrhosis, which is also the most common cause of ascites in North America and Europe. Moreover, hepatorenal syndrome may complicate other forms of liver disease besides alcoholic cirrhosis, but the pathogenesis in such circumstances may not be the same as in the cirrhotic state. (*J Natl Med Assoc.* 1992;84:153-162.)

Key words • renal failure • alcoholic cirrhosis • decompensated cirrhosis • hepatorenal syndrome

Most cases of functional renal failure in the United States occur in the setting of alcoholic cirrhosis,[1,2] which is also the most common cause of ascites in North America and Europe.[3,4] The present review is confined to the discussion of alcoholic cirrhosis and functional renal failure because hepatorenal syndrome may complicate other forms of liver disease besides cirrhosis,[5-8] but the pathogenesis in such circumstances may not be the same as in the cirrhotic state.[1]

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Functional renal failure may be broadly defined as renal dysfunction associated with liver disease that is unresponsive to conventional medical treatment; it may be relatively *stable*, characterized by steady blood urea nitrogen (BUN) and creatinine, and ascites and edema unresponsive to diuretic therapy, or it may be *unstable*, characterized by relentless, unexplained, rapid renal deterioration (hepatorenal syndrome).

The interrelationship between liver disease and renal dysfunction was recognized as long ago as the era of Hippocrates,[9] and severe oliguria occurring in hepatic disease and culminating in death was first reported by Flint in 1863.[10] In the 1920s, it was recognized that many liver diseases could cause dysfunction of an apparently normal kidney.[11] Helwig and Schutz[12] introduced the term hepatorenal syndrome in 1932 when they described a patient with renal failure and biliary tract disease.

Hepatorenal syndrome appears to be the most severe presentation of fluid and electrolyte disorder seen in alcoholic liver disease.[13,14] Despite the prevalence of this condition, and consistent with the present lack of understanding of its etiology, hepatorenal syndrome has no established effective treatment. Retrospective studies have shown that hepatorenal syndrome may be present in 17% of hospitalized decompensated cirrhotics and in more than 50% of cirrhotics who die.[15] Most cirrhotics with ascites refractory to therapy have the stable form of functional renal failure.[16]

DECOMPENSATED CIRRHOSIS

One of the hallmarks of cirrhosis is the tendency to retain sodium and an impaired ability to excrete free

water.[17,18] This propensity to retain sodium varies among individuals and is not simply caused by a reduction in the glomerular filtration rate (GFR).[16] Although the GFR tends to decrease as the cirrhotic state advances, normal and even supranormal GFR has been observed in some decompensated cirrhotics.[19,20] Head-out water immersion, a procedure that raises the GFR, does not guarantee normalization of sodium excretion,[21] so normal filtration does not preclude sodium retention.

Two hypotheses have emerged to explain sodium retention in decompensated cirrhosis: the "underfill" and "overfill" theories of ascites formation, neither of which alone can be correct. According to the underfill theory, increased portal pressure combined with decreased osmotic pressure lead to marked lymphatic "backup pressure" and eventual weeping of lymph from the surface of the liver into the peritoneum, with the consequent formation of ascites. This sequestration of fluid into the abdominal cavity then results in decreased cardiac output, decreased circulating volume, decreased GFR, and increased sodium retention. The relatively decreased circulating volume is then further compromised by arteriovenous shunting and splanchnic (as well as pulmonary and peripheral) vasodilatation.[14,21,22] The nature of the vasodilatory principles as well as the full complement of the volume receptors involved in the vasodilatory process are as yet undefined.[21] There is some experimental evidence, however, that portal hypertension does indeed induce generalized splanchnic vasodilation.[23,24] Portal decompression will decrease splanchnic plasma volume while total plasma volume remains elevated suggesting that nonsplanchnic vasodilatation exists as well.[25,26]

Evidence in favor of the underfill theory includes observations that maneuvers that increase circulating volume (head-out water immersion and peritoneovenous shunting) will often result in improvement of hormonal aberrations and, in many instances, also increase the subnormal GFR and raise the decreased cardiac output.[27-29]

There are several arguments against the underfill theory.[30,31] Compensated cirrhotics have normal or low plasma renin activity (PRA) and angiotensin II levels that are consistent with high, not low, circulating volume. In addition, compensated cirrhotics with high or normal cardiac output do not necessarily respond with diuresis and natriuresis to fluid loading or head-out water immersion. Finally, dog models with underfill (caval constriction) differ from models with bile-duct ligation or toxic cirrhosis in that the former have decreased cardiac output and increased vascular resistance while the latter have increased cardiac output and decreased vascular resistance.[32-34]

According to the overflow theory, plasma volume is theorized to be the first to expand because of primary renal sodium retention, and then because of increased portal and lymphatic pressures and local Starling forces, the peritoneum becomes destined to manifest fluid overaccumulation as ascites.[30,31]

In support of the overflow theory are observations that compensated cirrhotics given mineralocorticoids will develop ascites, suggesting that sodium retention and ascites formation occur despite apparently adequate circulating volume and GFR. In addition, spontaneous diuresis and natriuresis have been seen in decompensated individuals in the absence of changes in their nonsplanchnic vascular volume,[35,36] which contradicts the underfill hypothesis that "refilling" of the circulating volume is a prerequisite for amelioration of the decompensated state. Furthermore, research on cirrhotic dogs has shown that sodium retention occurs up to 10 days *before* ascites develops. The sodium retention is not relieved by portacaval shunting and is not related to conventionally studied parameters such as GFR, blood pressure, and hormone concentrations.

The nature of the stimulus that initiates excessive renal sodium retention as a "primary" event is not established, but it has been shown that acutely elevated portal pressure will effect renal sodium retention, which in turn may be diminished by renal denervation.[37] This finding suggests that intrahepatic baroreceptors that have been stimulated by increased sinusoidal pressure may cause efferent renal nerve activation via a central nervous system (CNS) integrative circuit, and effect subsequent avid renal sodium retention independently of the presence of ascites.[38] The underfill theory, however, cannot explain the diuretic and natriuretic response of decompensated cirrhotics to head-out water immersion, nor can it explain their elevated PRA, aldosterone, arginine vasopressin, and sympathetic amine concentrations. The theory also offers no explanation for the formation of A-V shunts and the presence of decreased vascular resistance in decompensation.

In reconciliation, both of the above theories have operative elements, and different factors may dominate depending on the phase of evolution of the cirrhosis.[30] A simplistic hypothesis would be that intrahepatic hypertension activates renal sodium retention initially, which subsequently predisposes to deposition of lymph in the peritoneum. It has been suggested that with

increasing ascites formation and concomitant development of A-V shunting and decreased vascular resistance, with a consequent reduction in effective volume, there would be an increase in sympathetic activity. This would lead to activation of the hormonal mechanisms designed to maintain circulating volume,[39,40] thus leading ultimately to the full-blown scenario of decompensated cirrhosis described below.

PATHOPHYSIOLOGY OF ASCITES FORMATION

Fluid flux across the hepatic sinusoids is determined principally by changes along their length.[30] Consequently, intrahepatic hypertension translates directly into hepatic sinusoidal hypertension. Transudation of fluid will at first be destined for the lymphatic vessels within the liver. As a compensatory response to this transudation, flow through the thoracic duct may increase up to 20 L per day.[41,42] If this capacity is overwhelmed, protein-rich fluid will then accumulate in the interstitium and weep from the surface of the liver into the peritoneum.[43]

In prehepatic (nonsinusoidal) portal hypertension, formation of ascites occurs less commonly.[44] When it does occur, the accompanying plasma oncotic pressure tends to be very low or the portal pressure very high. The contrasting propensities for ascites formation in sinusoidal and nonsinusoidal portal hypertension may exist because hepatic sinusoids compared to the splanchnic capillaries are much more permeable to albumin and protein. Moreover, the splanchnic vessels seem to have the ability to autoregulate their flow and consequently their intraluminal pressure.[45,46]

In cirrhotic patients, 60% to 80% of the mesenteric and splenic blood flows, respectively, are shunted through collateral circulation.[23,47] Despite this collateralization, hepatic flow is normal in these individuals[48]; therefore, total splanchnic flow must be markedly increased. In all probability, this increased flow is also a consequence of both arteriovenous shunting and vasodilatation, and it undoubtedly contributes to portal hypertension and partially explains persistence of the latter even in the presence of marked collateral drainage.[44]

FUNCTIONAL RENAL FAILURE: HEPATORENAL SYNDROME

Current knowledge does not permit prediction of which cirrhotic patients will develop functional renal failure. As stated previously, the renal failure may be stable with ascites refractory to medical treatment,[15,16] or it may be rapidly progressive (unstable or hepatorenal syndrome).

Stable functional renal failure may be defined as decompensated cirrhosis that is unresponsive to diuretic therapy. Hepatorenal syndrome may be defined as incompletely explained progressive renal failure in patients with liver dysfunction in the absence of clinical, laboratory, or anatomic evidence of other known causes of renal failure.[1,2,49] Early in hepatorenal syndrome, the features of prerenal insufficiency are present, but these are not responsive to volume expansion.[1,50] At times, the clinical picture may resemble acute tubular necrosis (ATN). The progression to ATN-like features in hepatorenal syndrome compared to progression in other conditions (septicemia) may sometimes be recognized by the extreme overall severity of the situation and the frequently observed long duration of the prerenal phase.[50] The hepatorenal syndrome has not been described in extrahepatic portal hypertension,[22] suggesting that intrahepatic sinusoidal hypertension is important in the pathogenesis of this condition.

Hepatorenal syndrome may occur spontaneously or apparently in response to some insult such as infection, hemorrhage, or overly vigorous diuresis.[15,50] The spontaneously occurring cases tend to progress slowly (and may present more like stable functional renal failure), while the induced cases tend to progress more rapidly. The classic patient with hepatorenal syndrome is a hospitalized alcoholic with severe liver disease, mild to moderate hypotension, ascites, avid sodium retention, and hepatic encephalopathy.[1,51] The frequent occurrence of hepatorenal syndrome during hospitalization may be explained in part by the gross underestimation of renal impairment in cirrhotics with ascites,[52] leading to overzealous diuresis and fluid restriction, and subsequent precipitation of the syndrome.

The renal circulation in hepatorenal syndrome demonstrates several abnormalities[1]:

- reduction of renal blood flow and glomerular filtration,[53,54]
- vasoconstriction involving the branches of the main renal artery and other smaller arteries,[55]
- cortical ischemia,[55] and
- instability.[55]

In regard to vasoconstriction and cortical ischemia, truncation of the arcuate and lobular arteries have been seen angiographically during life, while postmortem studies have demonstrated restoration of perfusion in these same channels.[55] In regard to instability, xenon washout studies have shown irregular filling and

drainage of the renal arteries. Gross and microscopic examinations of kidneys from patients with hepatorenal syndrome are usually normal. The reported reversals of clinical renal disease with liver transplantation[56,57] or with the transplantation of the failing kidney to a recipient with a normal liver[58] support the endorsement of functional renal failure[44] as a descriptive term for this renal impairment with liver disease.

The prognosis for hepatorenal syndrome is quite poor—documented recoveries usually occur only after improvement in liver function or after liver transplantation.[56,57] Because of the implied irreversibility of the condition, the diagnosis must be made with great care. Prerenal states that may mimic hepatorenal syndrome[59] and lead to misdiagnosis must be rigorously excluded.

There are two proposed explanations for the development of hepatorenal syndrome. The first is that the circulatory changes are actually a reflection of the kidney's physiological responses to abnormalities in the extrarenal circulation (splanchnic pooling and A-V shunting). Inherent in this explanation is the possibility that the kidney is unable to react entirely appropriately because of some underlying deficiency or dysfunction (such as lack of necessary prostaglandins). The second explanation proposes that some as yet unidentified humoral or neurohumoral agent directly causes the characteristic circulatory renal abnormalities.[1] This agent may be either a pathological entity or an excessively released physiological entity that is released from, or inadequately inactivated by, the diseased liver. Once the syndrome is fully established, exogenous volume replacement is unable to reverse the process and is seldom of lasting benefit.

ENDOCRINOLOGY OF CIRRHOSIS AND HEPATORENAL SYNDROME

Volume-Regulatory Hormones Other Than Atrial Natriuretic Peptide

Plasma Renin Activity, Aldosterone, and Angiotensin II. Most investigators agree that many decompensated cirrhotics have elevations of PRA and aldosterone, but that the significance of these elevations in the pathophysiology of the fluid and electrolyte disorder in these patients is unclear. For instance, head-out water immersion will result in suppression of aldosterone and PRA in decompensated cirrhotic patients, but they may or may not subsequently respond with diuresis or natriuresis.[21] In responders, head-out water immersion and spironolactone produce a much greater diuresis/natriuresis than spironolactone alone, suggesting that excess aldosterone is not the only cause of sodium and water retention. In addition, pharmacological doses of desoxycorticosterone acetate (DOCA) will not block diuresis or natriuresis induced by head-out water immersion, suggesting that the fluid and electrolyte disorder exists somewhat independently of the concentration of aldosterone.[60] An increased aldosterone level may be a factor of qualified importance, then, in decompensated cirrhotic patients; it apparently causes significant sodium retention in these individuals only when distal delivery of solute is adequate. Aldosterone assumes progressively less importance as GFR decreases to low levels often found in severely decompensated cirrhotic patients. In view of the above considerations, it is not surprising that spironolactone is usually adequate as a therapeutic agent in decompensated cirrhotics when their GFR is near normal. More severely decompensated cirrhotics whose excessive sodium retention is even less dependent on aldosterone-induced sodium resorption in the distal tubule will require loop diuretics, in combination with spironolactone for any diuresis/natriuresis to occur.

Plasma renin activity is often elevated in patients with decompensated cirrhosis.[61] In addition, angiotensin II-converting enzyme administration to such patients will lead to a fall in blood pressure and worsening of renal circulatory hemodynamics, suggesting angiotensin II dependency of blood pressure in such patients.[61] However, elevated PRA may not simply reflect a decrease in renal perfusion because some cirrhotics with elevated PRA may have normal or elevated GFR. In an attempt to explain the elevated PRA in the face of normal GFR, some investigators have suggested that a systemic hypotensive tendency is present in decompensated cirrhosis and is the cause of the elevated GFR.[62]

Arginine Vasopressin. Arginine vasopressin plays a major role in the abnormal handling of free water in patients with decompensated cirrhosis. Earlier investigations attributed the problem to reduced delivery of solute to the distal nephron consequent to increased proximal absorption of sodium[63,64] and to the decrease in GFR.[65] More recent studies, however, emphasize the possible role of excessive arginine vasopressin secretion in disordered free-water handling. For example, rats with experimental cirrhosis and no endogenous arginine vasopressin (Brattleboro rats) respond normally to a water load when compared to neurohypophysis-intact cirrhotic rats who are able to excrete only 58% of the load.[66]

Similarly, decompensated cirrhotics have either incomplete or no suppression of arginine vasopressin in

response to water-loading[31,67] and elevated basal levels of arginine vasopressin in more severely decompensated patients.[68] In experimental cirrhosis in rats, the free-water handling abnormality actually develops up to several weeks after the development of ascites,[69] suggesting that avid proximal sodium retention and excessive retention of free-water may be independently occurring phenomena. The hypersecretion of arginine vasopressin in decompensated cirrhosis is likely due to a decrease in effective circulating volume and is not due to osmotic stimuli. The reduction in effective volume is likely the result of splanchnic vasodilatation and decreased systemic vascular resistance that occurs in decompensated cirrhosis.

Catecholamines. Peripheral levels of catecholamines are often elevated in decompensated cirrhosis.[70,71] The increase in catecholamine concentration is explained by the underfill hypothesis on the basis of increased sympathetic activity consequent to decreased effective circulatory volume. The overfill hypothesis argues that the increased sympathetic activity is a reflection of efferent renal sympathetic neuron activity (ERSNA) caused by stimulation of intrahepatic sinusoidal baroreceptors. The therapeutic use of beta-blockers in decompensated cirrhosis has produced varied results,[72] perhaps because concomitant systemic sympathetic-blocking effects on cardiac output, blood pressure, and PRA cannot readily be dissected from renal sympathetic blocking effects per se.

What are the effects of increased ERSNA? The innervation to the kidney is exclusively noradrenergic and effects vasoconstriction of both afferent and efferent arterioles—there is no evidence for a vasodilation effect.[73] Renal nerve stimulation will cause increased renin and prostaglandin formation, and also will result in increased tubular reabsorption of sodium.[73] The latter effect is caused by norepinephrine-mediated stimulation of tubular epithelial cell sodium/potassium adenosinetriphosphatase (ATPase).[74,75] Increased renal sympathetic tone may also lead to a decrease in GFR, which, together with increased proximal sodium reabsorption, may result in decreased distal tubular sodium delivery and thus eliminate the mineralocorticoid escape phenomenon.[14,31]

Prostaglandins. The role of prostaglandins in decompensated cirrhosis has recently attracted much attention. In a dog model of chronic bile-duct-ligation cirrhosis, prostaglandin synthetase inhibitors will decrease GFR and renal blood flow,[76] indicating that locally synthesized prostaglandins are fundamental in renal function. Similarly, in patients with liver disease, prostaglandin synthetase inhibitors will decrease GFR. This decrease is most marked in avid sodium retainers. In cirrhotics who respond to head-out water immersion, urinary prostaglandin (PGE_2) excretion will increase up to three times more than in controls,[77] and this increase correlates well with sodium excretion. It is strongly felt by some investigators[78,79] that the increase in PGE_2 is a compensatory mechanism whereby cirrhotics with ascites and adequate renal function attempt to maintain renal blood flow, sodium excretion, and free-water clearance in an otherwise adverse hormonal milieu. Urinary prostaglandin excretion is increased by factors known to alter fluid and electrolyte balance in cirrhosis. Along these lines, renal nerve stimulation,[73] angiotensin II, norepinephrine, and arginine vasopressin all increase PGE_2 synthesis.[44,80-83]

It is not known if prostaglandins directly affect tubular sodium reabsorption. However, loop diuretics induce renal prostaglandin formation,[84] and prostaglandin synthetase inhibitors decrease the effects of loop diuretics, so it is plausible that local renal prostaglandin formation may mediate the natriuretic effect of these agents and participate in the regulation of sodium reabsorption.[44]

Bradykinin, Vasoactive Intestinal Polypeptide, and Prolactin. The hormones bradykinin, vasoactive intesinal polypeptide (VIP), and prolactin are of lesser importance in the pathogenesis of the abnormalities seen in cirrhotics. Bradykinin, a known vasodilator, could play some role in cirrhosis-related renal dysfunction. Decreased kallikrein in the plasma[85] and possibly urine[86] of cirrhotics does not establish a bona fide renal kinin deficiency because the plasma kallikrein-kinin system is distinct from the renal system. Vasoactive intestinal peptide concentrations are elevated in some cirrhotics, and infusion of VIP mimics some of the hemodynamic alterations seen in liver disease.[87,88] Because this hormone is elaborated in the intestine and degraded in the liver, it has been proposed that excessive circulating VIP levels may contribute to the renal abnormalities of cirrhosis. Prolactin concentrations are elevated in some cirrhotics, and this hormone has distinct effects on water and electrolyte handling in some animals. In man, however, its effects on water and electrolyte equilibrium are far from convincing, and it probably plays little, if any, role in the altered homeostasis of functional renal failure.

Cirrhosis and Atrial Natriuretic Peptide

Atrial Natriuretic Peptide. Atrial natriuretic peptide (ANP) is a hormone elaborated in the atrial

myocytes and is released in response to volume overload, which results in an increase in atrial wall tension or stretch.[89,90] The circulating form in humans is a 28-amino acid entity with potent natriuretic, diuretic, and vasoactive properties.[91] Specifically, the hormone causes an increase in GFR,[92] antagonizes the release and actions of arginine vasopressin,[93] and inhibits aldosterone and renin synthesis.[94,95]

Atrial Natriuretic Peptide in Cirrhosis. Several studies have looked at baseline ANP levels in cirrhotic animals and in cirrhotic patients. Our own animal data have suggested no difference in ANP concentrations in cirrhotic rats compared to normal controls.[96] Some studies in humans have shown that ANP levels in cirrhotic patients are either normal or slightly elevated[97-100] while others have demonstrated that ANP levels are elevated several-fold.[101-102] The marked variability of ANP concentrations between study groups and within study groups is not yet clear. The immunoreactivity of ANP may not always parallel its bioactivity, and oxidation of the C12-methionine group within ANP, for example, will alter activity of the circulating polypeptide.[103] Parenthetically, selected cardiac patients with very high plasma ANP concentrations have been discovered who harbor a different, perhaps less active, species of hormone, suggesting that a very rapid release of ANP may lead to incomplete processing of the hormone and abundant release of a "variant" less active polypeptide that results in high levels of immunoreactively measured hormone.[104] Only trace amounts of this entity have been found in cirrhotic patients, indicating that the elevations of ANP in cirrhosis reflect measurement of bioactively active hormone.[104]

There apparently is no absolute deficiency of ANP in cirrhosis. Because decompensated cirrhotic patients retain excessive amounts of salt and water, however, it appears that the observed elevations of ANP in these patients are not in themselves adequate to control the associated fluid and electrolyte disorder, and, like abnormal values of other volume-regulatory hormones, are probably reflective of the underlying pathological state.

The Endocrinology and Etiology of Hepatorenal Syndrome

As in decompensated cirrhosis without renal failure, PRA and angiotensin II may be elevated in hepatorenal syndrome,[105] but it does not appear likely that their elevation is the cause of the accompanying renal vasoconstriction. The administration of saralasin (an angiotensin II antagonist or weak agonist) or captopril does not definitively improve renal function in these patients,[106-108] indicating that elevated hormones are reacting to some other causative factors. Head-out water immersion will also decrease PRA in these patients without improving renal function significantly.[109,110]

Studies designed to investigate increased sympathetic activity in this disorder also suggest that increased sympathetic tone is not the primary cause of the syndrome. Intrarenal phentolamine was found not to reverse the renal vasospasm, although interpretation was somewhat confounded by an associated decrease in systemic blood pressure.[55] Injection of dihydroergocristine (an α-antagonist) did decrease renal resistance but urinary flow and urinary sodium changes were small.[111] In addition, renal denervation does not entirely block the antinatriuresis of liver injury in the dog,[112] and hepatorenal syndrome has been reported in a renal transplant patient with obviously abnormal sympathetic innervation in the transplanted organ.[113] Finally, when head-out water immersion does result in some improvement in creatinine clearance in hepatorenal syndrome, there is no correlation between renal improvement and norepinephrine levels.[24,114]

Prostaglandins have received considerable interest in the study of hepatorenal syndrome. Cirrhotic patients with hepatorenal syndrome have decreased urinary PGE_2,[108,115] but the significance of this decrease is not established. Low-dose, limited administration of prostaglandin synthetase inhibitors to cirrhotics apparently causes reversible renal failure,[116-118] suggesting that a prostaglandin deficiency may precipitate renal failure. Perhaps, in hepatorenal syndrome, the kidney is deficient in PGE_2 and is subject to the development of severe vasoconstriction.[115] A reported decrease in renal prostaglandin-endoperoxide synthase in hepatorenal syndrome suggests a possible cause of this putative prostaglandin deficiency.[119] At present, there is no evidence to support a causative role for vasoconstricting prostaglandins because, in at least one instance, specific blockade of thromboxane in hepatorenal syndrome patients with increased thromboxane metabolite excretion did not reverse the syndrome or result in clinical improvement.[108]

Excitement about the possible fundamental role of vasodilatory prostaglandins in the etiology of hepatorenal syndrome is dampened somewhat by studies that reported no benefit in the condition when PGA_1 was administered parenterally[120] or when PGE_1 was given intrarenally.[121] In addition, head-out water immersion has been reported to increase urinary PGE_2 excretion

without necessarily sustaining improvement in renal function.[77]

Another agent whose potential role in hepatorenal syndrome remains undefined is glomerulopressin. This hormone appears to be very important in regulating GFR in normal individuals. It has been shown that in vivo infusions of amino acids or glucagon will increase GFR, but in the isolated kidney they will not.[122] However, if one infuses glomerulopressin into the isolated kidney, GFR and renal blood flow will increase,[123] suggesting that glomerulopressin may actually mediate the effect of increasing GFR by protein meals, amino acid infusions, and glucagon administration. It is postulated that glomerulopressin, which is made in the liver, is made in insufficient amounts in liver disease, including hepatorenal syndrome. Our unpublished observations in cirrhotic rats support this hypothesis. Cirrhotic rats show a significantly lower level of glomerulopressin activity in the rat-stomach-fundus bioassay than do normal control or pair-fed animals.

Endotoxemia also has been suggested as a cause of hepatorenal syndrome. Endotoxins originating from gut bacteria may be found in normal portal blood and are thought to be inactivated in the liver specifically by Kupffer's cells.[124] It is plausible that a deceased liver may be unable to inactivate endotoxins, or alternatively, that the latter may escape the cirrhotic liver by traversing the collateral circulation. One study[125] has demonstrated positive endotoxemia in 30 of 43 cirrhotics with ascites. These 30 patients had decreased renal function, increased serum creatinine, and increased mortality. Furthermore, the greater the endotoxemia as measured by stimulus assay, the higher was the mortality.

Other possible causative agents in hepatorenal syndrome have been proposed. It has been shown that selective brain lesions in animals may cause renal failure,[126,127] so it is possible that hepatic encephalopathy may lead to derangement of the central nervous system, alteration of normal functional nervous control of blood vessels, and ultimately to the development of hepatorenal syndrome. Finally, false neurotransmitters (such as octopamine) may escape hepatic degradation in the diseased liver, be incorporated into neurons, and upon subsequent release, lead to the loss of adrenergic tone and eventual local renal vasoconstriction.

CONCLUSION

In cirrhosis, there appears to be an associated spectrum of fluid and electrolyte abnormalities. Patients with compensated alcoholic cirrhosis and intrahepatic sinusoidal hypertension may become prone to excessive sodium and water retention that at some point is no longer controllable by simultaneously activated physiological mechanisms. At that point in the clinical course, decompensated cirrhosis is identified, recognizable by the presence of ascites, edema, or both. Decompensated cirrhosis is often endocrinologically characterized by abnormal hormone concentrations, including elevations in PRA, arginine vasopressin, and aldosterone, and by alterations in prostaglandin secretion and release.

When decompensated cirrhosis no longer appears to be responsive to available treatment regimens, or in other words, when ascites persists despite sodium restriction and use of maximal diuretic therapy, the fluid and electrolyte abnormality has apparently evolved into functional renal failure, which may be relatively stable and indolent or may progress rapidly downhill and be recognizable as hepatorenal syndrome. At present, there is no proven effective therapy for this latter condition.

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